

Synthesis and solid-state structures of a macrocyclic receptor based on the 2,6-bis(2-anilinoethynyl)pyridine scaffold†

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A fluorescent macrocyclic anion receptor based on the 2,6-bis(2-anilinoethynyl)pyridine scaffold has been synthesized to investigate the mechanism of fluorescence quenching in this class of compounds. X-ray crystallography reveals that the binding pocket of the receptor is a natural host to both H₂O and HCl, accommodating either molecule in nearly identical environments. Our studies show that protonation, not collisional quenching, is responsible for the observed fluorescence quenching response.

The seminal crown ether studies of Pedersen in the mid-1960s heralded the importance of the field of artificial macrocyclic ion receptors.^{1,2} Much of the work in this area has been inspired by nature where many ionophores, such as valinomycin (Fig. 1, left), are preorganized with a specific size and shape to selectively bind ions.³ Since these pioneering discoveries, the field of macrocyclic receptors has expanded rapidly as advanced synthetic techniques, ranging from ring closing metathesis⁴ to molecular templating,^{5–7} have permitted access to a wide range of macrocyclic topologies in high yields.

Most of the early studies on macrocyclic ionophores focused on cations since they have relatively low energies of hydration, compared to anions, are less polarizable, and have predictable binding geometries. The first examples of macrocyclic receptors for anions (ionophores that are much less explored) appeared during the study of crown ether derivatives. Replacing one or more of the oxygen atoms with a more basic nitrogen afforded aza-crown macrocycles that exhibited a high affinity for anions upon protonation.⁸ This idea was expanded further by the study of azacryptands, where macrobicyclic, three-dimensional aza-crown ethers were designed to encapsulate

specific anions (Fig. 1, right).^{9,10} While these compounds were of great interest from a fundamental supramolecular standpoint, the early molecules lacked distinct spectral features for their different binding conformations. To have utility as an anion sensor, a receptor should ideally have easy to read spectral changes upon a binding event. Specifically, anion sensors that exhibit a fluorescence response have received considerable attention for their potential use in cellular imaging, pollution/hazard detection, and waste remediation.^{11–16}

Recently our team has focused on the synthesis and binding properties of a family of inherently fluorescent receptors based on the 2,6-bis(anilinoethynyl)pyridine scaffold.^{17–22} Interestingly, phenylurea derivatives substituted with electron-withdrawing groups (*e.g.*, **1a**, Fig. 2) displayed an “off-on” response in the presence of chloride, which typically quenches fluorescence.^{19,23} We hypothesized that in the absence of solvophobic aggregation, free rotation about the sp–sp² single bonds resulted in non-radiative decay of the molecule in its unbound state; however, anion binding could restrict rotation and afford increased conjugation *via* a nearly planar U-shaped conformation (Fig. 2).

Conversely, anion binding by receptors with electron-donating-substituted phenylureas (*e.g.*, **1b**) quenched fluorescence.

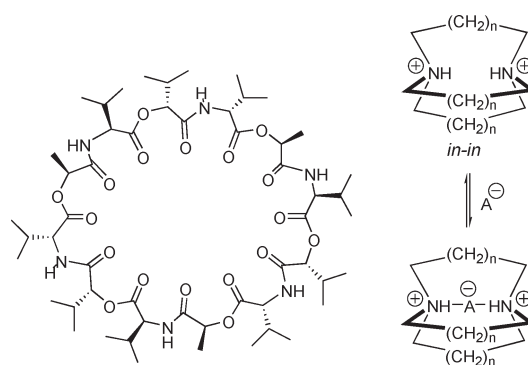


Fig. 1 Structures of valinomycin, a potassium ionophore (left) and a doubly protonated azacryptand binding an anion (right).

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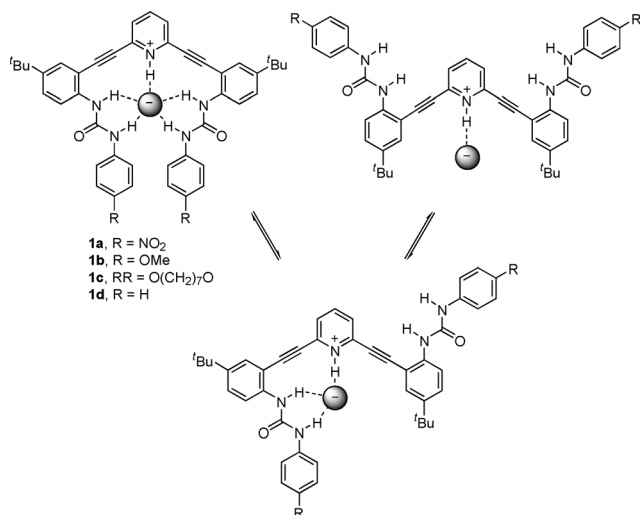
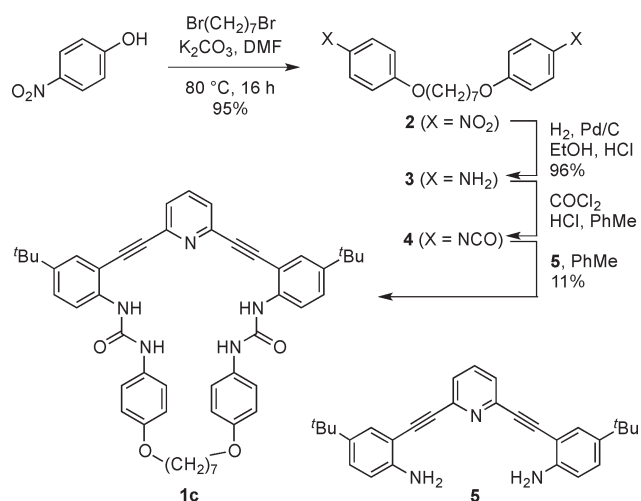


Fig. 2 Proposed binding conformations in 2,6-bis(2-anilinoethynyl)pyridine receptors.

This is likely associated with the less acidic nature of the urea hydrogens, but the exact mechanism of quenching was unclear. We speculated that a macrocyclic alkoxyphenylurea receptor such as **1c** would enforce the U-shaped conformation and thus limit the role of non-radiative decay in the observed fluorescence quenching. We report herein the synthesis of macrocycle **1c**, its excitation and emission spectra, and its solid state structure binding either H₂O or HCl.

The preparation of receptor **1c** is shown in Scheme 1. Williamson ether synthesis between 1,7-dibromoheptane and *p*-nitrophenol under basic conditions afforded bis-nitrophenyl compound **2**, which was reduced *via* catalytic hydrogenation to give bis-aniline **3**. Interestingly, when **3** was treated with triphosgene, yields of the desired bis-phenylisocyanate **4** were poor and unreliable. Counterintuitively, higher yields of **4** were obtained by first protonating **3** with anhydrous HCl followed by the addition of phosgene (as a solution in toluene), presumably due to slower reaction kinetics and reduced oligomerization.



Scheme 1 Synthesis of receptor **1c**.

Unstable **4** was concentrated under reduced pressure to remove excess phosgene and HCl and subsequently reacted with previously reported 2,6-bis(2-anilinoethynyl)pyridine core **5**^{17,22} to afford the desired macrocycle **1c** in low yield.

Colourless single crystals of **1c** were grown *via* slow evaporation from a CH₂Cl₂/hexanes solution. The resulting X-ray structure (Fig. 3, top) shows the desired macrocycle with an unanticipated water molecule bound within the cavity.²⁴ The urea hydrogens in each host form a tetradentate hydrogen bond network to the oxygen of the encapsulated water molecule; the pyridine nitrogen and urea carbonyls of neighbouring molecules accept the remaining hydrogen bond from the bound water molecule, resulting in an H-bonded 1-D chain within the crystal structure (Fig. 3, bottom). One of the H atoms from the water molecule and one of the H atoms from a urea group in **1c**·H₂O make intermolecular O–H...O and N–H...O H-bonds with O...O and N...O distances and angles at H atoms of 2.943(3) Å, 2.924(3) Å and 168(5)°, 169(2)°, respectively.

Gratifyingly, orange crystals of the HCl salt of **1c** were also obtained by bubbling HCl gas through a CHCl₃ solution of the macrocycle, which was then subjected to slow vapour diffusion of pentane at –25 °C.²⁵ The crystal structure (Fig. 4, top) shows the chloride anion stabilised by five H-bonds, similar to what was observed in the structures of parent phenylurea **1d**¹⁷ and a benzene-core analogue of **1b**;²⁶

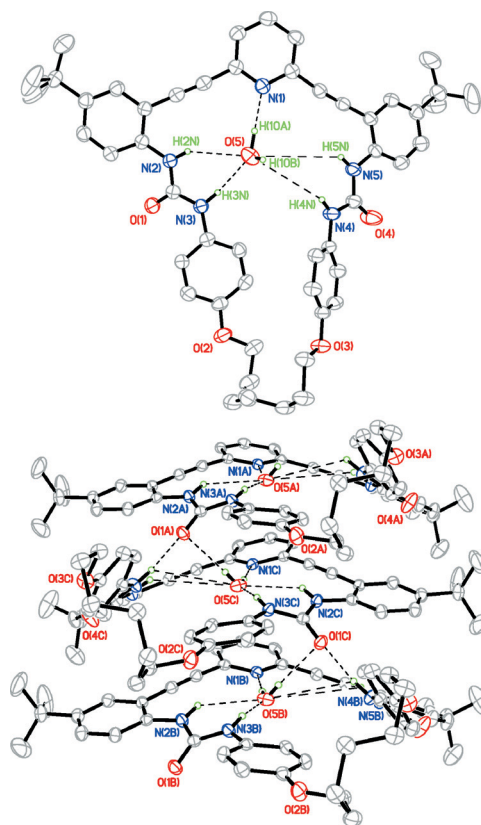


Fig. 3 Front view (top) and representative crystal packing (bottom) of **1c**·H₂O; non-coordinating H atoms and hexane solvent molecule omitted for clarity; ellipsoids drawn at the 50% probability level.



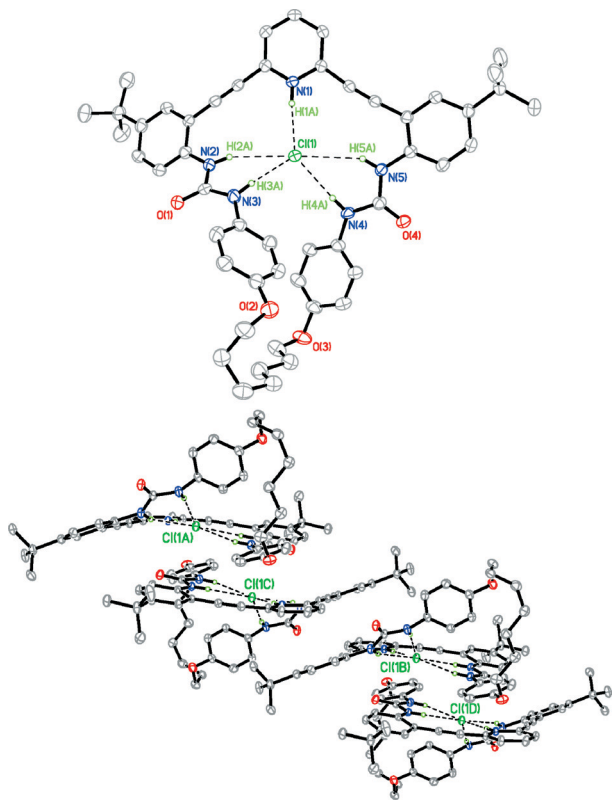


Fig. 4 Front view (top) and representative crystal packing (bottom) of **1c**·HCl; non-coordinating H atoms and solvent molecules omitted for clarity; ellipsoids drawn at the 50% probability level.

however, the urea N–H···Cl bond distances (Table 1) in **1c**·HCl are all shorter ($\Delta d = 0.023$ – 0.196 Å) than the analogous distances found in **1d**·HCl, clearly illustrating the tighter binding of chloride when encapsulated by the macrocycle. This result shows that the binding pocket can accommodate a molecule of either HCl or H₂O in the solid state along with minor changes in conformation, analogous to what was observed with our initial class of sulphonamide receptors.²⁰ Nonetheless, without the additional hydrogen bond donor found in the binding pocket of **1c**·H₂O, the crystal packing of **1c**·HCl is dramatically different: dimeric units form with intermolecular interactions dominated by van der Waals' forces (Fig. 4, bottom). The crystal structure of **1c**·HCl also includes a CHCl₃ solvent molecule that fills the empty space between these dimers.

Table 1 Selected NH···Cl distances^a

Bond	1c ·HCl	1d ·HCl ^b	Benzene-core analogue of 1b ·HCl ^c
N1–H1···Cl	3.025(3)	3.033(3)	3.579(3) ^d
N2–H2···Cl	3.500(3)	3.640(3)	3.523(3)
N3–H3···Cl	3.194(3)	3.227(3)	3.212(3)
N4–H4···Cl	3.194(3)	3.279(3)	3.214(3)
N5–H5···Cl	3.536(3)	3.600(3)	3.732(3)

^a Distances in Å between heavy atoms; atom numbering shown in Fig. 4. ^b Ref. 17. ^c Ref. 26. ^d C1–H1···Cl for benzene-core analogue of **1b**.

The neutral state of macrocycle **1c** is fluorescent with an emission band at 400 nm; however, when HCl is added the fluorescence is red shifted and significantly quenched (Fig. 5). Interestingly, if **1c** is protonated using an acid containing a non-coordinating counteranion (*e.g.*, HBF₄, which typically has a lower quenching proficiency than other anions),²⁷ the fluorescence is quenched to the same degree as with HCl. In line with the observed change in emission spectra, the excitation spectra of both **1c**·HCl and **1c**·HBF₄ are blue shifted from the neutral species **1c** by the same degree. These findings suggest that protonation plays the key role in the observed quenching behaviour instead of collisional quenching, as is typically encountered in the presence of halides. Furthermore, bound anions can affect the pK_a of adjacent functional groups, indicating that bis(arylethynyl)pyridines tailored to bind a specific anion could selectively trigger a protonation-based quenching response. This could allow for selective sensors that overcome typical Stern–Volmer quenching trends ($I^- > \text{CNS}^- > \text{Br}^- > \text{Cl}^- > \text{C}_2\text{O}_4^{2-} > \text{CH}_3\text{CO}_2^- > \text{SO}_4^{2-} > \text{NO}_3^- > \text{F}^-$). What is still unclear is why electron-withdrawn phenyl ureas display an “off-on” response in the presence of chloride.^{19,22} One would presume that quenching to some degree would be observed and investigation into this behaviour is ongoing.

In summary, we have disclosed the synthesis of macrocyclic receptor **1c** for comparison with its acyclic counterparts. X-ray structural analysis shows that chloride binding in the cavity of **1c** affords shorter hydrogen bonds and thus tighter binding within the pocket compared to its acyclic counterpart **1d**. The binding pocket of receptor **1c** is a natural host to both H₂O and HCl, accommodating either one in similar environments. Emission studies indicate that the quenching behaviour observed with electron donating substituents in this class of bis(arylethynyl)pyridine receptors is due to protonation and not collisional quenching. This could allow for selective quenching-based sensors that overcome typical Stern–Volmer quenching trends.

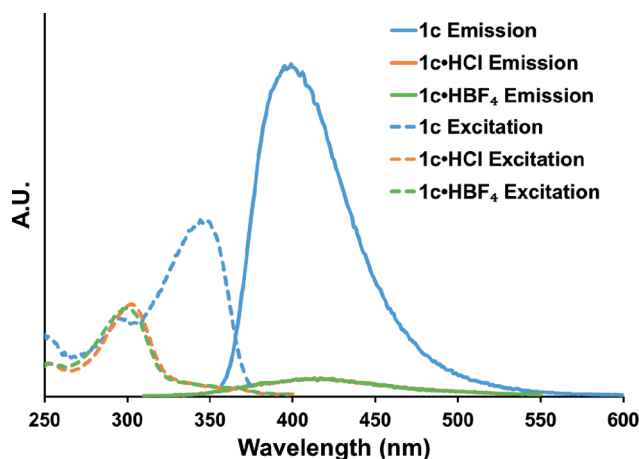


Fig. 5 Fluorescence excitation and emission spectra of receptor **1c** in CHCl₃ solution and the response upon exposure to selected acids. Neutral **1c** was excited at 347 nm and the protonated receptors at 300 nm.



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- 25 Crystallographic data for **1c**·HCl (CCDC 968267): C₅₆H₆₇Cl₄N₅O₄ [(C₅₀H₅₃N₅O₄)(HCl)(HCCl₃)(C₅H₁₂)], *M* = 1015.95, 0.19 × 0.06 × 0.02 mm, *T* = 100(2) K, monoclinic, space group *P2₁/n*, *a* = 14.6699(8) Å, *b* = 13.9019(8) Å, *c* = 27.0087(15) Å, β = 102.838(3)°, *V* = 5370.4(5) Å³, *Z* = 4, *D*_c = 1.257 Mg m^{−3}, *μ* = 2.392 mm^{−1}, *F*(000) = 2152, 2 θ _{max} = 135.66°, 37 694 reflections, 9580 independent reflections [*R*_{int} = 0.0531], *R*₁ = 0.0891, *wR*₂ = 0.2627 and GOF = 1.059 for 9580 reflections (577 parameters) with *I* > 2 σ (*I*), *R*₁ = 0.1023, *wR*₂ = 0.2771 and GOF = 1.059 for all reflections, max/min residual electron density +1.824/−1.053 e Å^{−3}.
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